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Treatment of Panic-Like Attacks with a Long-Acting Analogue of Somatostatin

JAMES L. ABELSON, MD, PHD, RANDOLPH M. NESSE, MD, AND AARON VINIK, MBBCH, FCP, MD

Department of Psychiatry, Anxiety Disorders Clinic, Department of Internal Medicine, Division of Endocrinology and Metabolism, and Department of Surgery, The University of Michigan, Ann Arbor, Michigan

Psychiatric evaluations were completed on four patients who were treated for "idiopathic flushing" with a long-acting analogue of somatostatin. All four patients had symptom profiles consistent with a diagnosis of panic disorder. All four experienced clinically significant relief from panic-like attacks while on the experimental medication. These findings suggest a possible role for somatostatin in the pathophysiology and treatment of panic disorder.
(J Clin Psychopharmacol 1990;10:128–132)

SOMATOSTATIN is a tetradecapeptide neurotransmitter and neuromodulator[1] that may be involved in the pathophysiology of neuropsychiatric disorders.[2–4] A long-acting, potent analogue of somatostatin (octreotide [SMS] or Sandostatin) has been shown to reduce the diarrhea and flushing produced by carcinoid tumors.[5,6] It also blocks attacks in nontumor patients with "idiopathic flushing."[7] Potential overlap between "idiopathic flushing" and panic disorder prompted a psychiatric review of the cohort of flushing patients described by Aldrich and associates.[7] This review suggested that the incidence of panic disorder within this group was higher than initially suspected. It also suggested that some patients with panic disorder, or a similar syndrome, were responding positively to treatment with SMS. This finding led us to collect new data on the four patients treated with SMS who appeared by chart review to have panic disorder. These patients received a semistructured psychiatric telephone interview and three of them agreed to face-to-face psychiatric evaluations using the Structured Clinical Interview for DSM-III-R (SCID).[8] Results of these detailed evaluations are summarized below. Summaries of the effects of SMS on flushing in these cases have appeared elsewhere.[7,9] Informed consent was obtained from all patients.

Received May 5, 1989 and accepted October 31, 1989. Address requests for reprints to Dr. Abelson, The University of Michigan, Med Inn, C405, Box 0840, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0840.

Case Reports

Case 1

A 34-year-old woman presented at age 30 with episodes of flushing, hot flashes, nausea, dizziness, and palpitations. From 15–25 years of age she had experienced mild, infrequent episodes of flushing and dizziness. At age 26 her episodes intensified and became characterized by the sudden onset of cutaneous flushing from the neck up, intense anxiety and an urge to "get out," racing and pounding heart, dizziness, trembling, feelings of unreality, tingling in her face, and fear that she was going crazy or losing control. The flushing usually spread over her trunk and limbs. In severe attacks the full symptom constellation would develop within minutes and could last up to an hour. At their worst, attacks occurred four or five times a day. The majority of her attacks were unexpected. At age 30 she became housebound for 2 months because of fear of attacks, and she became depressed and suicidal. She had a history of depression and drug/alcohol use but denied depression or substance abuse at the time her attacks increased in severity. Attacks continued despite full abstinence from alcohol and psychotropic drugs.

Her medical evaluation at age 30 included routine blood studies; head and adrenal CT scans; EEG; cardiac echocardiogram; urinary 5-HIAA, catecholamines, and metabolites; serum histamine; a gut-peptide hormone screen (plasma gastrin, vasoactive intestinal peptide, pancreatic polypeptide, somatostatin, substance P, and neurotensin); and a skin biopsy to rule out mastocytosis. No specific abnormalities were found. In subse-

quent follow-up she had intermittent, mild elevations of plasma gastrin, substance P, and vasoactive intestinal peptide (VIP). She was given a diagnosis of idiopathic flushing.

High-dose aspirin, given to inhibit prostaglandin production, decreased attack frequency and improved functioning. However, she continued to experience full-blown attacks on a weekly basis. Because of continuing attacks and concern about prolonged treatment with high-dose aspirin, she sought alternative treatments. Aspirin was discontinued and subcutaneous injections of SMS (50 μg twice a day) were begun. Her weekly attacks ceased almost immediately and she has not had a full attack in the subsequent 3 years. Mild episodes of flushing continued but at much reduced levels of subjective severity and frequency.[9] After full attacks ceased, she entered a 1-year individual psychotherapy program that helped stabilize her personal life. At age 33 she was able to discontinue SMS treatment without symptom recurrence. She has remained off all medication since and has noted only minor flushing and hot flashes associated with bright sun exposure. Avoidance behavior has resolved entirely and she is functioning effectively and successfully in a stressful professional position.

The SCID, administered 1 year after SMS discontinuation, resulted in lifetime diagnoses of: panic disorder with agoraphobia, in remission; major depressive disorder, in remission; alcohol dependence, in remission; and marijuana abuse, in remission. The only current diagnosis was generalized anxiety disorder.

Case 2

A 47-year-old homemaker was seen at age 42 for episodes of tremulousness, headache, palpitations, and flushing. She was well until age 39 when she noted episodic, spontaneous upper-body and facial flushing, associated with lightheadedness, tremulousness, headache, palpitations, sweating, and anxiety. Her episodes lasted from a few seconds to an hour and varied in frequency from a few per month to more than 10 per day. They initially seemed to be relieved by eating sugar, but when a medical work-up was negative and a hypoglycemia diet failed to produce lasting improvement, the patient was referred to a psychiatrist. Six months of individual and family psychotherapy provided no benefit. Convinced that she had a serious, undiagnosed medical problem, she sought further evaluation.

At age 42 her attacks were occurring 15–20 times per day and she was limiting her driving because she feared having an attack while behind the wheel. Endocrinological evaluation revealed fasting hypoglycemia; elevated plasma levels of somatostatin, motilin, and prostaglandin E_2; and borderline elevated levels of serotonin. Treatment with SMS 100 μg twice a day resulted in dramatic, dose-dependent improvement, which was reflected in patient reports and diary records. Diary-recorded subjective severity and frequency of attacks decreased rapidly.[9] Mean severity, rated on a four-point scale, fell from 3.0 to 1.0, and mean frequency fell from 10 to two per day. Days free of attacks increased from 0% to 92%. After 3 months, a saline placebo was single-blindly substituted for SMS. The patient initially reported no subjective change, although diaries revealed an increase in attacks. Eighty-two percent of days were attack-free during 3 months on SMS. Only 42% of days were attack-free during the first 2 weeks on saline. Ten months later symptoms had returned, both subjectively and by diary counts, to pretreatment levels. A second trial on SMS 50 μg twice a day was unsuccessful. The drug was discontinued, without return to the higher dose, because of her initial subjective report of no change on placebo.

She continued to have frequent attacks over the next 2 years. She developed increased restriction in her ability to drive alone, but reported that she "refused" to allow her life to be limited in any other way by the attacks. Alprazolam 0.5 mg three times a day was used intermittently to reduce attack severity. An SCID, administered 1 year after SMS discontinuation, resulted in a diagnosis of panic disorder with mild agoraphobia. A year after the SCID the patient had become even more restricted and finally agreed to psychiatric intervention. A clinical evaluation has just been completed and the current clinical diagnoses are panic disorder with moderate agoraphobia and histrionic personality disorder.

Case 3

A 31-year-old man was seen for recurrent headaches associated with flushing, diarrhea, epigastric burning, and palpitations. Episodes of unilateral headache, nausea, and flushing began at age 23. At age 24 he began to have loose, watery stools during episodes. Later that year he had his first "full-blown" attacks, consisting of headache, flushing, loose stools, epigastric burning, nausea, palpitations, shortness of breath, lightheadedness, shaking, sweating, and feelings of warmth. These attacks would come on suddenly and last 30–40 minutes, with the headache and diarrhea occasionally continuing for 3–6 hours afterwards. During his worst period he was having headache and flushing daily, associated with diarrhea 70% of the time. Full-blown attacks occurred weekly, 10% of which were unexpected. Many were associated with eating. Weakness and malaise forced curtailment of some activities, but he denied significant anxiety, fears, or avoidance behaviors. Symptoms of anergia, loss of libido, sexual dysfunction, and insomnia were noted. Diagnoses of migraine and atypical depression were made.

Prior evaluation included normal urinary 5-HIAA (twice), head CT, neck CT, and routine blood studies. Treatment attempts between ages 23–27 included ergotamine, alprazolam, imipramine, amitriptyline, protriptyline, trazodone, lithium, analgesics, β-blockers, calcium channel blockers, histamine blockers, clonidine, and anti-inflammatory agents. None of these produced significant and lasting benefits. The tricyclic trials were limited in duration or dose by side effects. Three years of individual psychotherapy provided general benefit but had no impact on his physical symptoms.

Evaluation at age 27 included plasma catecholamines, serotonin, calcitonin, and gut-peptide hormone screen; urinary histamine; and a pentagastrin stimulation test for release of neuropeptides. Results were all within normal limits. Initiation of SMS, 50 μg twice a day, resulted in almost immediate cessation of all attacks. Symptom diaries revealed that mild flushing continued, but episode severity fell from 4.0 to 1.0 and frequency fell from 4 to 1 per day.[9] After 4 months, SMS was discontinued and attacks recurred. Treatment was resumed with full resolution of symptoms. A second attempt at discontinuation 8

months later was successful. He remained well without medication for 4 months and then relapsed. Detailed medical evaluation was again unremarkable. SMS was resumed and he remained free of symptoms for 6 months. When SMS was discontinued a third time he remained free of symptoms, except for several mild attacks of flushing and headache in the past year. He is now functioning well in a professional capacity.

The SCID diagnosis was panic disorder without agoraphobia, in remission. He denied fear or anxious feelings during attacks but did report intense discomfort. The SCID also revealed a single episode of major depression that began a few months after beginning lithium (for headaches) and resolved within a month of discontinuing the lithium.

Case 4

A 39-year-old woman was seen at age 35 for episodes of flushing associated with low blood pressure. Episodes of facial flushing and gastrointestinal distress began at age 14. At age 19 she had a pyloric ulcer, which healed with treatment. She developed hypertension in her 20s, which was controlled with antihypertensive medication. At age 34 she began having "drop attacks" every few weeks during which she would feel lightheaded and flushed and would fall to the floor, without documented loss of consciousness. Self-monitoring revealed blood pressure as low as 60/40 during these attacks. She also began to note attacks of flushing, fear of fainting, palpitations, lightheadedness, sweating, nausea, fatigue, an overwhelming need to sit down and breathe deeply, and occasional loose stools. During these attacks she turned white and then red. These attacks occurred suddenly and spontaneously several times a week and lasted 10–20 minutes. Mild flushing with palpitations seemed to be precipitated by ingesting cheese, red wine, or liquor, but the patient could identify no precipitants for her full-symptom attacks. The patient denied severe anxiety during her initial attacks, but they were associated with a fear of fainting; and she soon began to experience fear that she might die in the midst of an attack. She also developed fear of having an attack while driving and curtailed her work activities and driving.

Prior evaluation had included repeated measurement of urinary 5-HIAA and catecholamines, as well as measurement of pituitary hormones, all of which had been normal. Subsequent studies included a gut-hormone screen, pentagastrin stimulation test, meta-iodobenzylguanidine scan, CT scan, urinary catecholamines, plasma catecholamines, and platelet norepinephrine. The only abnormality was mild elevation in substance P. Initiation at age 37 of SMS 50 μg twice a day reduced attack frequency. An increase to dosing three times a day led to full resolution of symptoms. Discontinuation of SMS after 16 months resulted in a slow return of full-blown attacks. She resumed treatment and attacks again resolved. Several further attempts to discontinue SMS have resulted in symptom recurrence. She has never had a major episode while on SMS.

The patient denied any prior history of anxiety, depression, mood swings, sleep or appetite disturbance, or contact with a mental health professional. She has received no other treatment and was unwilling to participate in a SCID.

Discussion

All four of these patients qualify, by DSM-III-R criteria, for the diagnosis of panic disorder. All four had dramatic responses to SMS, with rapid cessation of chronic, debilitating attacks. In two cases relapse occurred with drug discontinuation, and reinstatement of treatment again provided symptom relief. The two patients who were able to discontinue SMS without relapse had obtained psychotherapy and made major life changes.

Generalizations from these cases must be made with caution. Although DSM-III-R criteria were met, significant diagnostic uncertainty remains. Except for the prominent flushing, cases 1 and 2 had presentations typical for panic disorder, but cases 3 and 4 appear more atypical. Diarrhea (case 3), for example, has been thought to be unusual in panic disorder. However, several reports suggest that episodic diarrhea may be part of a panic disorder-like syndrome that responds to traditional antipanic agents.[10, 11] Hypotension (case 4) is common in patients with "idiopathic flushing" but rare in panic disorder. However, patient 4's hypotensive episodes may well have been secondary to her antihypertensive medication. She was in the midst of adjustments in her antihypertensive regimen when her "drop attacks" began. These two patients also minimized their subjective-cognitive symptoms of anxiety. However, such minimization is not unusual when patients with panic disorder present to nonpsychiatric medical settings.[12–14] Case 4 described herself as someone who never got frightened, but nevertheless began to significantly restrict her activities out of fear of attacks.

All four of these patients experienced significant flushing that justified their treatment with SMS. Flushing is listed among the diagnostic characteristics of panic attacks, but the incidence of observable flushing in panic disorder is unknown. Skin temperature is probably the best physiological marker of flushing and two studies have reported increased skin temperature during panic attacks.[15, 16] This presumably reflects vasodilation and contrasts with laboratory studies of induced anxiety, where vasoconstriction is seen.[17, 18] Skin temperature changes in panic attacks merit further exploration to see if vasodilation occurs and to determine whether it is due to autonomic changes or to the presence of vasoactive substances, such as substance P or VIP. Elevations in vasoactive peptides were noted in some of the patients described here. To our knowledge, there have been no studies of these peptides in panic disorder. Whether features such as prominent flushing, peptide elevations, diarrhea, and hypotension differentiate our patients from typical panic patients and limit the implications of their response to SMS cannot be determined from the data

presented here. Prospective trials in patients with typical panic disorder are needed.

If SMS does block panic, its mechanism of action may be revealing. The possibility that SMS might block panic via effects on the hypothalamic-pituitary-adrenal (HPA) axis is suggested by the following: (a) oversecretion of corticotropin-releasing hormone (CRH) may mediate panic;[19] (b) low CSF somatostatin levels are associated with increased HPA axis activity;[2, 20] (c) somatostatin inhibits both the corticotropin (ACTH) response to CRH[21] and the CRH response to stress[22] and is thought to inhibit ACTH, cortisol, and catecholamine release through its role as an inhibitory neuromodulator of hypothalamic CRH;[23] and (d) inhibition of CRH may be the mechanism by which other agents exert their antipanic effects.[24] It is not yet known, however, whether SMS crosses the blood-brain barrier and inhibits HPA axis activity in man. It does suppress growth hormone release from the pituitary[25] and ectopic ACTH release from a medullary thyroid carcinoma;[26] but it does not acutely block ACTH or cortisol responses to insulin-induced hypoglycemia.[25] Other mechanisms that could potentially explain effects of SMS on panic include interactions with catecholaminergic[20, 23, 27] and GABA-ergic systems.[1, 20] SMS also inhibits a number of vasoactive neuropeptides, such as substance P and VIP,[5, 7] that could mediate somatic symptoms of panic.

The cases presented here are mainly of heuristic value. These patients do not all have typical panic disorder; their symptom relief may or may not be attributable to SMS and our discussion of mechanisms is highly conjectural. The cases should, however, stimulate interest in some novel areas. "Idiopathic flushing," skin temperature changes in panic, vasoactive peptides in anxiety disorders, and the role of somatostatin in anxiety disorders are all topics that merit further scientific attention. Somatostatin has potential clinical as well as scientific utility. Despite substantial advances in pharmacological treatments for panic disorder, there remain patients whose attacks are difficult to control with available agents. In addition, currently available agents have delayed onset of action and bothersome side effects, or have problems with dependence and withdrawal. SMS could provide a significant addition to our antipanic armamentarium. On both clinical and scientific grounds, cautious, placebo-controlled trials of SMS in patients with panic disorder are warranted.

Acknowledgments

Supported in part by a grant from the National Institute of Health to the University of Michigan Clinical Research Center (RR-00042) and by Sandoz Pharmaceuticals, New Jersey.

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